REMARKS

Status of the Application

Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 are pending in the present application. Applicant notes that the Examiner inadvertently omitted to mention that Claims 19 and 20 are pending in the application.[1] These claims were not cancelled by Applicant. Indeed, Claims 19 and 20 were listed as pending in Appendix II of Applicant's prior Amendment and Response which was mailed to the Office on September 5, 2001. Also, Claims 19 and 20 were rejected in the instant Office Action,[2] reflecting the Examiner's recognition that they remain pending.

The Specification has been amended to reflect abandonment of the prior provisional application, and to correct a grammatical error.

The Examiner objected to the Specification on the ground that it does not "reflect the abandonment of the provisional application."[3] Applicant has made appropriate amendment.

Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 have been rejected on the following grounds:

1. Claim 2 continues to be rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness;

2. Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, and 80-120 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676);

3. Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714);

4. Claims 80-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §102(e) for alleged anticipation by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714) and Pytela *et al.*;

5. Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714), Thorpe, and Pytela *et al.*;

---

[1] Office Action Summary page, item 4; and Office Action, page 2, item 1.

[2] Office Action, page 9, item 8; and page 13, item 9.

[3] Office Action, page 20, item 13.

6. Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714);

7. Claims 80-86, 90-96, and 110-116 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description;

8. Claims 86, 96, and 116 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description; and

9. Claims 80-120 stand rejected under 35 U.S.C. §112, first paragraph, for alleged non-enablement.

Applicant believes that the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

1. Rejection Of Claim 2 Under 35 U.S.C. §112, Second Paragraph

Claim 2 continues to be rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness of the term "substantially."[4] Applicant respectfully must disagree.

In the prior response which was mailed to the Office on September 5, 2001 (hereinafter, referred to as "Applicant's prior response"), Applicant argued that this term is definite because the Specification provides a mathematical range (*i.e.*, at least about two-fold, five-fold, and ten-fold) as well as a control (*i.e.*, specificity for $\alpha 5\beta 1$) to apprise the artisan of the exemplary preferred mathematical ranges for binding of the ligand to $\alpha 5\beta 1$ integrin, as compared to binding of the ligand to another integrin. The Examiner found this not "persuasive because the statements within the specification, drawn to range, are not *limiting*."[5] However, the Examiner is respectfully reminded that the test of definiteness is **not** whether or not the Specification's ranges are limiting. Rather,

> "A decision as to whether a claim is invalid under [§112 ¶2] requires a determination whether those skilled in the art would understand what is claimed."[6]

---

[4] Office Action, page 2, item 4.

[5] (Emphasis added) Office Action, page 2, last paragraph.

[6] *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1217 , 18 USPQ2d 1016 (Fed. Cir. 1991).

Under the proper inquiry, the enclosed Declaration by Dr. Virgil L. Woods demonstrates that the term "substantially" is understood by one skilled in the art. Dr. Woods is qualified to speak on the level of ordinary skill in the fields of integrin biology and biochemistry.[7] Based on the Specification's teachings, Dr. Wood's Declaration concludes that it is his "understanding that Claim 2's recitation of an agent which 'does not substantially interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$ integrin' means that the agent's interference with the specific binding of $\alpha 5\beta 1$ integrin to a ligand is at least two-fold greater than the interference of the agent with the specific binding of another integrin to its cognate ligand."[8] Because the term "substantially" is clear to one skilled in the art, this term is definite.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claim 2 under 35 U.S.C. §112, second paragraph.

2. Rejection Of Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, And 80-120 Under 35 U.S.C. §102(e) Over Pasqualini *et al.*

Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, and 80-120 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676).[9] Applicant respectfully traverses because the Examiner continues to fail to meet her burden of establishing anticipation. Moreover, any alleged inherency is rebutted by Applicant's additional evidence which is submitted herewith.

A. Anticipation Is Not Established

The Examiner is respectfully reminded that the law recognizes **only two principles** for anticipation, *i.e.*, express anticipation and anticipation under the doctrine of inherency. The Federal Circuit has clearly enunciated this legal standard as follows:

---

[7] Declaration by Dr. Woods, item 1.

[8] Declaration by Dr. Woods, item 4.

[9] Office Action, page 3, item 5.

> "Anticipation is established *only* when a single prior art reference discloses, *expressly or under principles of inherency*, each and every element of a claimed invention."[10]

However, as discussed in more detail below, both express and inherent anticipation continue to be absent.

1. Express Anticipation Is Lacking

Applicant previously advanced the following three arguments in support of the position that there is no express anticipation: (1) Since the Examiner conceded that Pasqualini *et al.* does **not** disclose an "agent that interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand," then Pasqualini *et al.* cannot expressly anticipate any of the rejected Claims 1-5, 9-13, 55-6, 68, 69, 71, 72, and 75 which recite this limitation,[11] (2) because the Examiner admitted that Pasqualini *et al.* "does not specifically state that the . . . ligand is fibronectin," then this is a further reason why Pasqualini *et al.* cannot anticipate Claim 3 which recites that "the ligand is fibronectin," and (3) since the Examiner admitted that Pasqualini *et al.* fails to disclose Claim 2's limitation that the "agent does not substantially interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$," then it cannot expressly anticipate Claim 2 for this additional reason.

The Examiner responded with two arguments. First, the Examiner argued that "the ligand of the prior art is a form of fibronectin, that is a multimeric form, which *binds to the claimed integrin receptor.*"[12] However, this argument suffers from the glaring problem of ignoring the legal requirement that express anticipation:

> "requires the disclosure in a single prior art reference of *each element* of the claim under consideration."[13]

---

[10] (Emphasis added) *RCA Corp. v. Applied Digital Data Sys., Inc.*, 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984).

[11] Applicant's argument is equally applicable to newly rejected Claims 80-120.

[12] (Emphasis added) Office Action, page 5, lines 8-10.

[13] (Emphasis added) *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 960, 148 USPQ 298, 301, adopted, 149 USPQ 640 (Ct. Cl. 1966).

Pasqualini *et al.* fails to **expressly disclose** the claims' limitation that **superfibronectin** "interferes with specific binding of the α5β1 integrin to a ligand expressed in the tissue." In other words, the Examiner's assertion that sFN binds to the claimed α5β1 integrin is based on conjecture. The Examiner is respectfully invited to point out where, if at all, such disclosure appears in Pasqualini *et al.*

Additionally, the Examiner's argument omits to consider the claims' further limitation that the agent's interference with the specific binding of α5β1 integrin to a ligand **results** in "reducing or inhibiting angiogenesis." While Pasqualini *et al.* discloses that sFN inhibits angiogenesis, there is **no express disclosure** that inhibition of angiogenesis is **caused** by the interference of sFN with the specific binding of α5β1 to a ligand expressed in the tissue, as recited by the claims. The Examiner is invited to show, with specificity, where Pasqualini *et al.* **expressly discloses** a causative connection between the unsubstantiated interference by sFN with α5β1 integrin's binding to a ligand, on the one hand, with the observed reduction in angiogenesis, on the other hand. Since two of the claims' limitations are **not expressly** disclosed by Pasqualini *et al.*, this reference cannot expressly anticipate.

The Examiner's second argument was that "although Applicant was invited to submit objective evidence demonstrating that the claimed method is functionally different than that taught by the prior art and to establish patentable differences, this evidence has not been submitted."[14] The Examiner is respectfully reminded that "A person *shall be* entitled to a patent *unless* "anticipation is established by the **Examiner**.[15] Thus, the Examiner's argument turns the burden of proof on its head by requiring **Applicant** to submit evidence of lack of anticipation, when the law instead requires the **Examiner** to provide evidence of anticipation. Under the law, "a person *shall be* entitled to a patent *unless*" anticipation is established by the Examiner.[16] Since the Examiner admitted that the claimed invention was not expressly described by Pasqualini *et al.* (as discussed above), then **express anticipation is lacking**, and Applicant need not show a thing.

---

[14] Office Action, page 4, lines 18-20.

[15] (Emphasis added) 35 U.S.C. §102(e)(2).

[16] (Emphasis added) 35 U.S.C. §102(e)(2).

2. Applicant's Prior Evidence Supporting Lack of Inherent Anticipation Is Not Rebutted

Because express anticipation is lacking, the Examiner must resort to anticipation under the doctrine of inherency. Under this doctrine,

> "the Examiner *must* provide *a basis in fact and/or technical reasoning* to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art."[17] "Inherency . . . may *not* be established by *probabilities or possibilities*. The mere fact that a certain thing *may* result from a given set of circumstances is *not sufficient*."[18]

In other words, in order to establish inherency, the Examiner needs to show that the alleged inherent limitation **must** result from the practice of Pasqualini *et al.*'s methods. It is not enough that the alleged inherent limitation **may possibly**, or even **probably**, result from Pasqualini *et al.*'s methods. The following discussion demonstrates that none of the Examiner's arguments establishes inherency, and that these arguments are contradicted by Applicant' previously submitted evidence as well as the additional evidence which is further discussed below.

The Examiner argued that because sFN "is a multimeric form of fibronectin, the superfibronectin would be expected to bind to a fibronectin receptor, known to be alpha 5 beta 1 and that binding would *by its very nature* would interfere with the specific binding of alpha 5 beta 1 integrin to another ligand . . ."[19] However, the inquiry under inherency is not whether sFN would "by its very nature" interfere with the specific binding of $\alpha 5\beta 1$ integrin to a ligand. Rather, the proper inquiry is whether Pasqualini *et al.*'s use of sFN **necessarily (not probably)** results in the recited "interference with specific binding of the $\alpha 5\beta 1$ integrin to a

---

[17] (Emphasis added) MPEP § 2112, citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990); see also *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

[18] *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

[19] Office Action, sentence bridging pages 4 and page 5.

ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue." Analysis under the proper inquiry precludes inherency for at least three reasons.

Prior to elaborating on these reasons, Applicant illustrates the proper application of the doctrine of inherency as analyzed by the Federal Circuit in *Glaxo Inc. v. Novopharm Ltd.*[20] In that case, Glaxo's patent claimed Form 2 rantidine hydrochloride. Novopharm argued inherent anticipation because Novopharm's practice of a prior art process always yielded the claimed Form 2 rantidine hydrochloride in 13 repetitions of the prior art process. However, because Glaxo obtained a different form (Form 1) of rantidine hydrochloride when they performed the same process, the Court found that the claimed Form 2 was **not inherently anticipated** since practicing the prior art process **could** yield crystals of **either** form.

The facts here are similar to those in *Glaxo*. As argued in Applicant's prior response, Pasqualini *et al.* does **not necessarily** disclose the limitation of "agent that interferes with specific binding of the α5β1 integrin to a ligand," or of "reducing or inhibiting angiogenesis" by such an agent because the prior art suggests **alternative mechanisms** for sFN action which do **not** implicate α5β1 integrin. In support of this position, Applicant previously pointed out that Pasqualini *et al.* expressly discloses the existence of alternative pathways for the action of sFN,[21] and also submitted several prior art references in support of their position that α5β1 integrin is only one of several receptors (such as α3β1,[22] α4β1,[23] αvβ1,[24] α4β7,[25] and αvβ3[26]) to which fibronectin binds. Based on this evidence, Applicant previously argued that since

---

[20] *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, en banc suggestion declined (Jun 21, 1995).

[21] "Whereas cells attach to fibronectin through integrin, cell attachment to sFN is mediated by both *integrins and other distinct receptors.*" (Emphasis added) Pasqualini *et al.*, column 1, lines 60-63.

[22] Takada *et al.* (1988), Takada *et al.* (1987), and Elices *et al.* (1991); attached as Tab 1 of Applicant's prior response.

[23] Masumoto & Hemler (1993), attached as Tab 2 of Applicant's prior response.

[24] Zhang *et al.* (1993), attached as Tab 3 of Applicant's prior response.

[25] Ruegg, *et al.* (1992), attached as Tab 4 of Applicant's prior response.

[26] Orlando R and Cheresh D (1991), attached as Tab 5 of Applicant's prior response.

not one, but several **alternative** mechanisms exist for Pasqualini *et al.*'s postulated anti-angiogenic action of sFN, it follows that sFN does **not necessarily** "interfere with specific binding of the α5β1 integrin to a ligand," as recited by each of the rejected claims. In other words, Pasqualini *et al.*'s inhibition of angiogenesis **could be** caused by interference of sFN with the binding of any one of α3β1, α4β1, αvβ1, α4β7, and αvβ3 (but **not** α5β1) with their cognate ligands. Because nothing in Pasqualini *et al.* teaches that inhibiting angiogenesis necessarily results by interferences with the binding of α5β1 (rather than any one of α3β1, α4β1, αvβ1, α4β7, and αvβ3) to a ligand, inherency is not established.

In responding to Applicant's above argument, the Examiner **admitted** that interference of Pasqualini *et al.*'s sFN with the specific binding of α5β1 integrin to a ligand is "*not* the *only possible* method."[27] This alone negates anticipation by inherency, because the Examiner is admitting that sFN's interference with the specific binding of α5β1 integrin to a ligand is only a **possible** method by which sFN causes inhibition of angiogenesis. However, the law is that :

"Inherency . . . may *not* be established by *probabilities or possibilities.*"[28]

In other words, the Examiner misapplies the proper legal test of inherency by persisting to engage in the very kind of "possibility" which the Federal Circuit has found **insufficient** to establish inherency.

In response to Applicant's above argument, the Examiner also argued that "since *fibronectin* is specific for alpha 5 beta 1, *it* would also be expected to bind with greater affinity and avidity to that integrin as opposed to other integrins and given the indefinite nature of the term 'substantially', *it* would not be expected to substantially interfere with specific binding of a ligand to an integrin other than alpha 5 beta 1."[29] The Examiner is

---

[27] (Emphasis added) Office Action, page 6, line 3.

[28] *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

[29] Office Action, page 5, lines 3-7.

respectfully requested to explain what nexus, if any, this argument has to alleged anticipation of the claims by Pasqualini *et al.*, since this reference uses superfibronectin, **not** fibronectin as referred to in the Examiner's argument.

The Examiner further argued that "Applicant admits on the record that sFN interferes with the binding of 5 different receptors on endothelial cells, *including alpha 5 beta 1*, to their respective ligands and for the reasons set forth above, sFN would interfere with specific binding of a ligand to alpha 5 beta 1 integrin."[30] This argument is factually incorrect. Contrary to the Examiner's assertion, Applicant did **not** state "that sFN interferes with the binding of . . . alpha 5 beta 1" to its ligand. Rather, Applicant provided evidence which shows binding of sFN to the $\alpha 3\beta 1$, $\alpha 4\beta 1$, $\alpha v\beta 1$, $\alpha 4\beta 7$, and $\alpha v\beta 3$ receptors which are **different from** $\alpha 5\beta 1$.

Furthermore, the Examiner's argument reflects a fundamental misunderstanding of the law of inherency. Even if sFN interfered with the binding of $\alpha 5\beta 1$ integrin to a ligand, this is **not enough** to establish inherency. Instead, the proper legal analysis requires the Examiner to rebut Applicant's evidence by demonstrating that Pasqualini *et al.*'s inhibition of angiogenesis by administration of sFN **cannot be caused** by interference with the binding of any one of the $\alpha 3\beta 1$, $\alpha 4\beta 1$, $\alpha v\beta 1$, $\alpha 4\beta 7$, and $\alpha v\beta 3$ receptors to their ligands, and is therefore **necessarily** caused **only** by interference with the binding of $\alpha 5\beta 1$ integrin to its ligand(s). The Examiner has not provided any evidence to support such a rebuttal. Accordingly, Applicant's argument stands uncontradicted, thus negating inherency.

Applicant also argued in the prior response that inherency is negated because of the **opposite biological effects** of sFN (which the Examiner speculates to be equivalent to the recited "agent that interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand") as compared to agents which are known to interfere with the specific binding of $\alpha 5\beta 1$ integrin to its ligand(s). Specifically, Applicant showed that in contrast to Pasqualini *et al.*'s disclosure that sFN **inhibits** cell migration on collagen,[31] the instant Specification teaches that inhibiting the specific $\alpha 5\beta 1$ integrin binding to a ligand "did **not affect** endothelial cell migration on

---

[30] (Emphasis added) Office Action, page 5, lines 17-21. See also, page 5, lines 21-22 which states "Applicant again admits on the record that sFN binds to the alpha 5 beta 1 integrin receptor."

[31] Pasqualini *et al.*, Figure 7; column 12, lines 37-44; and column 25, lines 9-14.

. . . collagen."[32] Based on this, Applicant argued that because Pasqualini *et al.*'s administration of sFN yields a **conflicting biological effect** when compared to the effect of agents that are known to interfere with the specific binding of the α5β1 integrin to a ligand, then it must be concluded that Pasqualini *et al.*'s sFN **cannot be equated** with the recited "agent that interferes with specific binding of the α5β1 integrin to a ligand." Thus, Applicant argued that the conflicting biological effects of sFN, versus an agent that interferes with the specific binding of the α5β1 integrin to a ligand, **refute** any improper inference that Pasqualini *et al.*'s administration of sFN **necessarily** results in the recited interference with the specific binding of α5β1 integrin binding to a ligand.

In response, the Examiner argued that "Applicant is arguing limitations not recited in the claims as currently constituted."[33] This is incorrect. The Examiner is invited to explain more clearly what "limitations" she is referring to.

Furthermore, the Examiner's argument demonstrates that she did not understand that the thrust of the scientific evidence is that there is a **functional difference** between the biological effects of sFN and the recited "agent" and that these differences refute the Examiner's allegation of equivalency of sFN to the recited "agent." In other words, if Pasqualini *et al.*'s sFN were equivalent to the recited "agent," then sFN would be **expected** to function similarly to the recited agent by **not inhibiting** cell migration on collagen. However, Pasqualini *et al.*'s own data demonstrates a **contrary** biological effect for sFN. Based on this evidence, Applicant reiterates that Pasqualini's administration of sFN **cannot** (let alone "necessarily") result in "interference with specific binding of the α5β1 integrin to a ligand."

The Examiner further argued that "the specification broadly defines the term 'peptide' as a polymer of amino acids that are linked by peptide bonds and for the reasons previously set forth this definition is not limiting and sFN meets the limitation of *this claim* since it is a polymer of amino acids that are linked by peptide bonds."[34] Applicant first notes that with the exception of claims 13, 14, 106, 107, 117, and 118 which recite that the agent is a "peptide," none of the other claims is so limited. Second, even if sFN were a peptide, it does

---

[32] Specification, page 45, lines 9-16.

[33] Office Action, page 6, lines 1-2.

[34] (Emphasis added) Office Action, page 6, lines 7-10.

not fall within the scope of the claims because it does **not necessarily** interfere with specific binding of α5β1 integrin to a ligand for the reasons explained above.

In view of the above, inherency is lacking based on (1) Applicant's evidence, and the Examiner's concession, of the existence of **alternative mechanisms** for the action of sFN action which do **not** implicate interference with the specific binding of α5β1 integrin to a ligand, (2) Applicant's evidence of **functional differences**, *e.g.*, that sFN has an **opposite biological effect** on cell migration on collagen as compared to the effect of agents which are known to interfere with the specific binding of α5β1 integrin to a ligand, and (3) the Examiner's misapplication of the legal test of inherency by continuing to improperly speculate on Pasqualini *et al.*'s disclosure.

B. Additional Evidence Further Rebutting Inherency

The Examiner invited Applicant to "submit objective evidence to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method."[35] Applicant believes that the above evidence alone negates inherency. Nonetheless, in order to expedite Applicant's business interests and allowance of the claims, Applicant submits the following additional evidence.

Yi *et al.*[36] proposes mechanisms of action for sFN which do not include α5β1 integrin. Yi *et al.* states that:

> "the mechanism of the *antiangiogenic* activity of [antiangiogenic substances that are derived by modifying ECM, such as sFN] *is unknown*."[37]

In other words, the **art-skilled** authors and reviewers of Yi *et al.* concluded, based on their collective knowledge and skill in the art, and having the benefit of an additional one-and-a-half years of experimentation **after** the issue date (July 13, 1999) of the Pasqualini et al. patent, that the art continues to be ignorant of **any** mechanism for the antiangiogenic activity of sFN, much less that the mechanism "necessarily" involves the recited interference with

---

[35] Office Action, sentence bridging pages 5 and 6; and page 6, lines 12-14.

[36] Yi *et al.* (2001) "A fibronectin fragment inhibits tumor growth, angiogenesis, and metastasis," Proceedings of the National Academy of Sciences, USA 98(2):620-624; attached at Tab 1.

[37] Yi *et al.*, page 624, paragraph bridging columns 1 and 2.

binding to α5β1 integrin. Because the Examiner is **not** "one skilled in the art,"[38] her conjecture of the inherency of sFN's interference with α5β1 binding cannot stand in the face of the skilled artisans's (*i.e.*, the authors and peer reviewers of the Yi *et al.* reference) opposing views that such a mechanism is not one which is recognized by those skilled in the art.

Furthermore, Yi *et al.* expressly advanced two hypotheses for the mechanism of action of sFN, neither of which involves interference with α5β1 integrin binding. The first hypothesis is that:

> "the antimetastatic activities of sFN observed in the previous study depended on a *mechanism other than antiangiogenic activity*. Preliminary data suggest that that effect is related to *accelerated removal of tumor cells* from the circulation."[39]

The above teaching stands for the proposition that Pasqualini *et al.*'s sFN reduces metastasis by impacting **tumor cells**, not **endothelial cells** (which are involved in the recited angiogenesis). Nothing is said about interfering with α5β1 integrin biochemistry. To the contrary, Yi *et al.*'s second hypothesis **points away from α5β1 integrin** and toward αvβ3 integrin, as follows:

> "we propose a common mechanism of action *in vivo* for the known antiangiogenic protein fragments [such as sFN]: they polymerize an arginine-glycine-aspartic acid-containing protein, the resulting polymers bind to the *αvβ3 integrin* on *angiogenic endothelial cells*, and the polymers inhibit cell proliferation and cause apoptosis. The polymers possibly act by affecting ECM formation or by arginine-glycine-aspartic acid-mediated activation of intracellular capases."[40]

Stated differently, Yi *et al.* suggests that, to the extent endothelial cells are involved, sFN acts via αvβ3, **not** α5β1. This squarely refutes inherency.

Additionally, the prior art demonstrates that Pasqualini *et al.*'s HT29 cells **do not express α5β1 integrin**. Pasqualini *et al.* shows that a one-time exposure of HT-29 carcinoma

---

[38] *Stratoflex, Inc. v. Aroquip Corp.*, 218 USPQ 871, 879 (Fed. Cir. 1983).

[39] (Emphasis added) Yi *et al.*, page 623, second column.

[40] Yi *et al.*, page 624, column 2.

cells to sFN inhibits tumor cell metastasis.[41] Varner *et al.*[42] demonstrates the **absence** of $\alpha5\beta1$ expression on HT29 cells by immunocytometry[43] and corroborates this absence by showing failure of HT29 to adhere to fibronectin.[44] Thus, even if the Examiner argued that Pasqualini *et al.*'s inhibition of HT29 metastasis were associated with inhibition of angiogenesis, the absence of $\alpha5\beta1$ expression on HT29 cells is evidence that the reduced metastasis which was observed by Pasqualini *et al.*'s administration of sFN, and the conjectured inhibition of angiogenesis, **cannot possibly** (much less "necessarily") be mediated by sFN's interference with the binding of $\alpha5\beta1$ integrin to a ligand. This unambiguously refutes inherency.

The art also shows functional distinctions between the biological effects of sFN and of fibronectin which further corroborate Applicant's earlier evidence that the biological effects of Pasqualini *et al.*'s sFN may be mediated by receptors other than $\alpha5\beta1$. Indeed, the publication of Morla *et al.*[45] is aptly entitled "Superfibronectin is a *functionally distinct* form of fibronectin." More specifically, Morla *et al.* teaches that:

> "As CHO cells bind to fibronectin with the $\alpha5\beta1$ integrin, whereas UCLA-P3 cells use the $\alpha v\beta5$ integrin as a fibronectin receptor, this indicates that *each of these integrins serves as a receptor of* . . . [superfibronectin]. [T]he superadhesiveness of cells on . . . [superfibronectin] may be due to binding of the cells through more than one class of receptors: integrins and a family of receptors not related to the integrins. This is in *sharp contrast* to the binding of cells to regular fibronectin, which is mediated entirely by integrins."[46]

From this teaching, it is clear that the biological effects of Pasqualini *et al.*'s administration of sFN are **not necessarily** mediated via $\alpha5\beta1$ integrin, but rather **may** be channeled through

---

[41] Pasqualini *et al.*, sentence bridging columns 18 nd 19; and Figure 3C-1, 3C-2.

[42] Varner *et al.* (1995) "Integrin $\alpha5\beta1$ expression negatively regulates cell growth: reversal by attachment to fibronectin," Molecular Biology of the Cell 6:725-740; attached at Tab 2.

[43] Varner *et al.*, page 728, Figure 1B.

[44] Varner *et al.*, page 728, second column; and page 729, Figure 2A.

[45] Morla *et al.* (1994) "Superfibronectin is a functionally distinct form of fibronectin," Nature 367:193-196; attached at Tab 3.

[46] (Emphasis added) Morla *et al.*, paragraph bridging pages 195 and 196.

other receptors. Because the Examiner does **not explain** how to **exclude** the probability that sFN inhibits angiogenesis by interfering with thes non-integrin receptors rather than by interfering with integrins, much less the α5β1 integrin, then Morla *et al.* further demonstrates lack of inherency.

The art further shows an additional functional difference between the effect of Pasqualini *et al.*'s sFN and the claimed invention's "agent" on cell migration on fibronectin and collagen. Pasqualini *et al.* demonstrates that sFN suppresses cell migration on both fibronectin **and** collagen when it states that "after preincubation with sFN, tumor cells are unable to spread or migrate on any of the immobilized human extracellular matrix proteins *fibronectin*, laminin, *collagen IV*, and vitronectin or on BSA."[47] In contrast, agents which inhibit specific binding of α5β1 to fibronectin inhibit cell attachment to **only** fibronectin, not to collagen. For example, Kim *et al.*[48] demonstrates that antibodies directed against integrin α5β1 inhibited migration of endothelial cells on fibronectin but not on collagen.[49] This additional functional difference shows that Pasqualini *et al.*'s sFN does **not necessarily** function as the recited "agent."

Applicant respectfully again draws the Examiner's attention to Applicant's earlier-submitted evidence which was discussed *supra*, and which shows a **material functional difference** between Pasqualini *et al.*'s sFN and the recited "agent" in connection with their effect on cell migration on collagen. In particular, the evidence shows that sFN **inhibits** cell migration on collagen.[50] In contrast, the instant Specification shows that inhibiting the specific binding of α5β1 integrin to a ligand "did **not affect** endothelial cell migration on . . . collagen."[51] Since Pasqualini *et al.*'s sFN **cannot function** as the recited "agent," Pasqualini *et al.* does **not necessarily** disclose the recited "agent."

---

[47] Pasqualini *et al.*, column 3, lines 17-22; and Figure 7.

[48] Kim *et al.* (2000) "Regulation of angiogenesis *in vivo* by ligation of integrin α5β1 with the central cell binding domain of fibronectin," Am. J. Pathol. 156(4):1345-1362; attached at Tab 4.

[49] Kim *et al.*, page 1353, paragraph bridging columns 1 and 2; and Figure 4D.

[50] Pasqualini *et al.*, Figure 7; column 12, lines 37-44; and column 25, lines 9-14.

[51] Specification, page 45, lines 9-16.

Because Pasqualini *et al.*'s inhibition of metastasis by administering sFN does **not** expressly or inherently disclose the limitation of "agent that interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand," it follows that this reference also must fail to disclose the limitation of "reducing or inhibiting angiogenesis." Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, and 80-120 under 35 U.S.C. §102(e) over Pasqualini *et al.*

3. Rejection Of Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, And 120 Under 35 U.S.C. §102(e) Over Pasqualini *et al.*

Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714).[52] Applicant respectfully traverses.

The Examiner is respectfully reminded that using multiple references in making a rejection under 35 U.S.C. §102 is proper only

> "when the extra references are cited to: (A) Prove the primary reference contains an 'enabled disclosure,' (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent."[53]

Since neither enablement nor the meaning of a term are in issue, the only proper reason for the Examiner's use of Ruoslahti *et al.* is to show alleged inherency of a characteristic in Pasqualini *et al.* Accordingly, Applicant's following arguments and evidence address Ruoslahti *et al.* in the context of inherency.

A. Inherency Is Not Established

The Examiner argued that Ruoslahti *et al.* shows that "the claimed method *appears to be the same* as that of the prior art method [of Pasqualini *et al.*] absent a showing of

---

[52] Office Action, page 6, item 6.

[53] MPEP §2131.01.

unobvious differences."[54] This reflects a continued lapse in observing Federal Circuit law that:

"Inherency . . . may *not* be established by *probabilities or possibilities*."[55]

The Examiner's persistence in arguing that the claimed method and Pasqualini *et al.*'s methods "appear to be the same" is precisely the type of analysis which the Federal Circuit has rejected for establishing inherency. Accordingly, inherency is not established.

The Examiner cited *Ex parte Novitski*[56] in support of her argument that Pasqualini *et al.* "will inherently lead to reducing or inhibiting angiogenesis" because "the prior art comprises the same method steps as claimed in the instant invention."[57] However, *Novitski* is factually distinguishable from the instant case. In *Novitski*, the claim in dispute recited "A method for protecting a plant from plant pathogenic nematodes which comprises the step of inoculating a plant with a nematode-inhibiting strain of *P. cepacia* which strain colonizes said plant." This claim was found to be inherent in the prior art of Dart *et al.* which discloses a method comprising the step of inoculating a plant with *Pseudomonas cepacia* type Wisconsin 526, which colonizes the plant. Inherency was found in *Novitski* because Novitski's specification described *P. cepacia* type Wisconsin 526 as inhibiting nematodes. Importantly, there was **no** evidence that the prior art's *P. cepacia* type Wisconsin 526 could have protected plants by a mechanism other than by being the recited "nematode-inhibiting" strain.

Unlike Novitski where alternative mechanisms for the cited prior art's bacteria were not shown, the prior art in the instant case demonstrates **alternative mechanisms** for sFN action which do **not** implicate $\alpha 5\beta 1$ integrin. This evidence shows that it is **probable** that Pasqualini *et al.*'s sFN inhibition of angiogenesis is caused by sFN's interference with the

---

[54] (Emphasis added) Office Action, page 7, lines 14-18.

[55] *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

[56] *Ex parte Novitski*, 26 USPQ 1389 (BPAI 1993).

[57] Office Action, page 8, second paragraph.

binding of any one of α3β1, α4β1, αvβ1, α4β7, and αvβ3 (but **not** α5β1) to their ligands. Thus, in order to rebut Applicant's evidence and to establish inherency, the Examiner must provide evidence or scientific reasoning which demonstrates that this probability is absent. This has not been done. Accordingly, inherency remains un-established.

B. Ruoslahti *et al.* Rebuts Inherency In Pasqualini *et al.*

Ruoslahti *et al.* rebuts, rather than confirms, inherent anticipation by Pasqualini *et al.* The Examiner admitted that Ruoslahti *et al.* "*does not specifically state* that the agent of the method binds alpha 5 beta 1 integrin at least two-fold, [*sic.*] five-fold, ten fold greater than any other integrin [such as] alpha V beta 3."[58] However, she averred that this reference provides evidence of inherency because "given that alpha 5 beta 1 is the fibronectin receptor, it would be expected that *fibronectin* not only selectively binds to alpha 5 beta 1 but also that it is specific for alpha 5 beta 1 and that thus all of the limitations of the claims are met."[59]

This argument suffers from at least three problems. Foremost among them is that it discusses a characteristic of Ruoslahti *et al.*'s **fibronectin** without providing a nexus of how this characteristic is extrapolated to the primary reference's **superfibronectin** (which is a structurally and functionally different molecule) without any evidence or scientific reasoning. Applicant further notes that fibronectin and superfibronectin are functionally distinct as further discussed below in Applicant's rebuttal evidence.

Secondly, Ruoslahti *et al.* rebuts inherency because it suggests that Pasqualini *et al.*'s sFN functions by inhibiting the **attachment** of **tumor cells**[60] to fibronectin, rather than by the recited "reducing or inhibiting angiogenesis." The Examiner is respectfully reminded of her position that sFN is a peptide.[61] Accordingly, Ruoslahti *et al.*'s teachings with respect to **peptides** are arguably applicable to sFN. In particular, Ruoslahti *et al.* unequivocally demonstrates that administering peptides which inhibit binding to α5β1 is associated with

---

[58] Office Action, page 7, lines 14-18.

[59] (Emphasis added) Office Action, page 7, lines 11-14.

[60] The tumor cells used were the B2/α27 cells, C8161 cells, MG-63 cells, and WI-38 cells, "which all express α5β1." Ruoslahti *et al.*, paragraph bridging pages 31 and 32.

[61] Office Action, page 6, last sentence.

inhibiting the **attachment** of **tumor cells**[62] to fibronectin.[63] In other words, Ruoslahti *et al.* suggests that peptides (including Pasqualini *et al.*'s sFN) function by an entirely different mechanisms (*i.e.*, inhibiting **cell attachment** rather than reducing **angiogenesis**) and on an entirely different target cell (*i.e.*, **tumor** cells as compared to **endothelial** cells) from peptides used in the instantly claimed methods. Because Ruoslahti *et al.* suggests a mechanism which is **different and distinct** from the recited "reducing or inhibiting angiogenesis" for Pasqualini *et al.*'s sFN, then it follows that "reducing or inhibiting angiogenesis" does **not necessarily** flow from Pasqualini *et al.*'s use of sFN. Thus, Ruoslahti *et al.* negates inherency of the claimed invention in Pasqualini *et al.*

Third, Ruoslahti *et al.*'s disclosure could not possibly be extrapolated to the effect of an agent on angiogenesis because every single experiment conducted by Ruoslahti *et al.* used **tumor cell lines**[64] which were devoid of **endothelial cells**, and because it is endothelial cells (not tumor cells) which are involved in angiogenesis. Accordingly, Ruoslahti *et al.*'s disclosure does not supplement that which is absent from Pasqualini *et al.* with regard to a role for any agent (let alone Pasqualini *et al.*'s sFN) in angiogenesis.

C. The Prior Art Further Rebuts Inherency

The Examiner suggested that evidence "that the claimed method is functionally different than that taught by the prior art" would overcome this rejection.[65] Applicant incorporates herein her above-discussed evidence which was used to rebut inherency by Pasqualini *et al.* and which shows that (1) Pasqualini *et al.*'s HT29 cells **do not express α5β1 integrin**, (2) the effects of using sFN by Pasqualini *et al.* are **not necessarily** mediated via α5β1 integrin, but rather **may** be channeled through other receptors, (3) sFN suppresses cell

---

[62] The tumor cells used were the B2/α27 cells, C8161 cells, MG-63 cells, and WI-38 cells, "which all express α5β1." Ruoslahti *et al.*, paragraph bridging pages 31 and 32.

[63] Ruoslahti *et al.*, Figures 5 and 11; page 5, lines 24-25; page 6, fifth paragraph; page 31, lines 11-34; and page 32, lines 1-8.

[64] For example, Ruoslahti *et al.* used the cell lines designated as B2/α27, B2/C1, C11, NIH 3T3, A375-M, B2/v7, HT-29, and IMR-90. Ruoslahti *et al.*, page 28, first paragraph.

[65] Office Action, sentence bridging pages 7 and 8.

migration on both fibronectin **and** collagen in contrast to agents which inhibit specific binding of $\alpha 5\beta 1$ to fibronectin, and which inhibit cell attachment to **only** fibronectin, not to collagen and (4) sFN **inhibits** cell migration on collagen in contrast to agents which inhibit the specific binding of $\alpha 5\beta 1$ integrin to a ligand and which do **not affect** endothelial cell migration on collagen.

In view of the above, inherency is not established and if arguably established, it is rebutted by the secondary reference of Ruoslahti *et al.* and by Applicant's additional evidence. Accordingly, Applicant respectfully requests that the rejection of Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, and 120 under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* be withdrawn.

4. Rejection Of Claims 80-106, 108-117, 119, And 120 Under 35 U.S.C. §102(e) Over Pasqualini *et al.*

Claims 80-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §102(e) for alleged anticipation by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714) and Pytela *et al.*[66]

The Examiner's arguments in support of this rejection are **identical** to those advanced in rejecting Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, and 120 under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* as evidenced by Ruoslahti *et al.*[67] with the exception that the Examiner added that "Pytela specifically teaches that alpha 5 beta 1 is selective for fibronectin."[68] However, Pytela *et al.*'s disclosure does not add to the deficient disclosures of either Pasqualini *et al.* or Ruoslahti *et al.* for the reasons discussed *supra*, and because Pytela *et al.* relates to fibronectin, not to Pasqualini *et al.*'s sFN. Applicant incorporates herein her above arguments and evidence in connection with overcoming the rejection of Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, and 80-120 under 35 U.S.C. §102(e) over Pasqualini *et al.*, and of Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, and 120 under 35 U.S.C. §102(e) over

---

[66] Office Action, page 8, item 7.

[67] Office Action, item 6 beginning on page 6.

[68] Office Action, page 8, last paragraph.

Pasqualini *et al.* as evidenced by Ruoslahti *et al.*, and respectfully requests withdrawal of the rejection.

5. Rejection Of Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, And 120 Under 35 U.S.C. §103(a) Over Pasqualini *et al.* In View Of Ruoslahti *et al.*, Thorpe, And Pytela *et al.*

Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714), Thorpe,[69] and Pytela *et al.*[70] Applicant respectfully traverses because a *prima facie* case of obviousness is not established. Furthermore, even if a *prima facie* case is arguably made, it is rebutted by Applicant's evidence.

A. A *prima facie* Case Of Obviousness Is Not Made

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish **any** one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicant to withdrawal of the rejection of the claims in issue.[71] Applicant urges that the Examiner has failed to establish not one, but **all three** requirements as discussed below.

Applicant notes that this ground of rejection is advanced for the first time in the instant Office Action. However, since the Examiner indicated that Applicant's arguments in their prior response to the rejection of Claims 1-5, 9-14, 19, 20, 55-72, and 75 under 35

---

[69] Thorpe (1985), "Monoclonal Antibodies," in "Biological and Clinical Applications," Pinchera *et al.* Eds., pp. 475-506.

[70] Pytela *et al.* (1985) Cell 40:191-198; Office Action, page 9, item 8.

[71] See, *e.g.*, *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

U.S.C. §103(a) over Pasqualini *et al.* in view of Ruoslahti *et al.* and Thorpe[72] "are relevant to the instant rejection,"[73] Applicant's following response to the new ground of rejection refers to her arguments in the prior response and also advances new arguments and evidence.

1. The Combined References Fail To Disclose All The Limitations Of The Claims

It is axiomatic for establishing a *prima facie* case of obviousness that "all the claim limitations must be taught or suggested by the prior art."[74] However, the Examiner has not established that the combined references disclose the limitations of an "agent that interferes with specific binding of the α5β1 integrin to a ligand" and that this interference causes "reducing or inhibiting angiogenesis,"as recited by each of the rejected claims.

a. Pasqualini *et al.* Fails To Disclose All The Claims' Limitations

With respect to each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75, Applicant previously argued that sFN of the primary reference of Pasqualini *et al.* is not an agent which "interferes with specific binding of the α5β1 integrin to a ligand" thereby reducing "angiogenesis" because (as explained *supra*) (1) the effects observed by Pasqualini *et al.* when administering sFN may be mediated by several receptors **other than** α5β1 integrin as evidenced by Pasqualini *et al.*'s own data which demonstrates an opposite effect when administering sFN (*i.e.*, inhibiting cell migration on collagen), as compared to the effect when interfering with the specific binding of the α5β1 integrin to a ligand (*i.e.*, no inhibition of cell migration on collagen), (2) Pasqualini *et al.*'s inhibition of metastasis may be mediated by inhibiting the **attachment** of **tumor cells** to fibronectin, instead of inhibiting **angiogenesis** by **endothelial cells**, as evidenced by Ruoslahti *et al.*'s teachings, and (3) Pasqualini *et al.*'s inhibition of **metastasis** is neither an express nor inherent disclosure of reducing **angiogenesis**

---

[72] Office Action mailed on March 9, 2001, page 8, item 10.

[73] Office Action, page 12, third paragraph.

[74] MPEP § 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

which is recited in each of the previously rejected Claims 1-5, 9-13, 19, 20, 55-72, and 75, and newly rejected Claims 80-106, 108-117, 119 and 120.

The Examiner was not persuaded "for the reasons set forth above" in the Office action.[75] The Examiner is invited to reconsider her conclusion in view of Applicant's above-discussed additional arguments and evidence rebutting anticipation by Pasqualini *et al.*

b. Ruoslahti *et al.* Does Not Provide The Elements Which Are Absent From Pasqualini *et al.*

Applicant previously argued that the secondary reference of Ruoslahti *et al.* does not bridge the gap of Pasqualini *et al.* since both references are silent on the limitations of "reducing or inhibiting angiogenesis" by using an agent which "interferes with specific binding of the α5β1 integrin to a ligand." Applicant argued that these limitations do **not necessarily** flow from Ruoslahti *et al.*'s disclosure because (1) Ruoslahti *et al.*'s inhibition of angiogenesis relates to using a peptide which binds to **αvβ3**, not to one which inhibits the specific binding of the recited "**α5β1**" to a ligand, (2) Ruoslahti *et al.* discloses inhibiting **metastasis** of tumor cells, not reducing or inhibiting the recited "**angiogenesis**," and (3) Ruoslahti *et al.*'s peptides which inhibit binding to α5β1 do so by inhibiting tumor cell[76] **attachment** to fibronectin,[77] not by the recited reducing or inhibiting "**angiogenesis**," and by impacting **tumor cells** rather than **endothelial cells** (which participate in the recited "angiogenesis").

The Examiner did not respond to any of the above arguments. Accordingly, the validity of these arguments, and Applicant's assertion that Ruoslahti *et al.* fails to disclose "reducing or inhibiting angiogenesis," stand un-rebutted.

---

[75] Office Action, page 12, last paragraph.

[76] The tumor cells used were the B2/α27 cells, C8161 cells, MG-63 cells, and WI-38 cells, "which all express α5β1." Ruoslahti *et al.*, paragraph bridging pages 31 and 32.

[77] Ruoslahti *et al.*, Figures 5 and 11; page 5, lines 24-25; page 6, fifth paragraph; page 31, lines 11-34; and page 32, lines 1-8.

c. Thorpe Fails To Supplement The Missing Limitations

Applicant previously argued that, like Pasqualini *et al.* and Ruoslahti *et al.*, the secondary reference of Thorpe also fails to disclose an agent which "interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand" thereby reducing "angiogenesis" because this reference relates to conjugating cytotoxins to peptides, not to agents which impact $\alpha 5\beta 1$ integrin and/or angiogenesis.

The Examiner responded that "Applicant has argued and discussed the references individually without clearly addressing the combined teachings."[78] This argument reflects a blatant disregard for the U.S. Supreme Court's express holding in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) that the analysis under of obviousness under 53 U.S.C. §103 **must include** an inquiry of "the scope and content of the prior art" and the "differences between the claimed invention and the prior art."[79] In conformance with controlling U.S. Supreme Court law, Applicant has addressed both these necessary factual inquiries under the "all elements" prong of a *prima facie* case of obviousness by beginning the analysis with what each of the references individually discloses. This was then followed by analyzing the deficiency of the primary reference and why **combining** its teachings with those of the secondary references does not add up to a disclosure of all the recited limitaitions. Thus, the Examiner's contention is wrong, and Applicant's analysis conforms with the legal requirements.

Since the Examiner has not rebutted Applicant's substantive argument with respect to Thorpe, the validity of this argument stands conceded.

---

[78] Office Action, page 12, last paragraph.

[79] *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) (holding that determination of obviousness requires a factual determination of (1) the scope and content of the prior art, (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness).

d. Pytela *et al.* Does Not Provide The Absent Limitations

The Examiner included Pytela *et al.* as a secondary reference in the new rejection under obviousness. But Pytela *et al.* does not provide the elements which are absent from the remaining references because Pytela *et al.* relates only to the identification of integrin $\alpha 5\beta 1$ as a cell surface receptor for fibronectin, and that $\alpha 5\beta 1$ integrin generally is selective for fibronectin,[80] and **not** to agents which reduce angiogenesis by interfering with the specific binding of $\alpha 5\beta 1$ to a ligand. Accordingly, combining the teachings of Pytela *et al.* with those of Pasqualini *et al.*, Ruoslahti *et al.* and Thorpe continues to fail to disclose the limitations of an agent which "interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand" thereby reducing "angiogenesis."

In view of the combined references' failure to disclose each of the limitations of the rejected claims, the first prong of a *prima facie* case of obviousness is not established. This alone necessitates withdrawal of the rejection of the claims under 35 U.S.C. §103.

2. The Combined References Do Not Provide A Motivation To Practice The Recited Combination Of Steps

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the reference to arrive at the **claimed invention**.[81] In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed."[82]

With respect to each of the previously rejected Claims 1-5, 9-13, 19, 20, 55-72, and 75, Applicant previously argued that there is no motivation for "reducing or inhibiting

---

[80] Specification, page 13, lines 3-6.

[81] *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

[82] (Emphasis added) *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *Robotic Vision Systems Inc. v. View Engineering Inc.*, 51 USPQ2d 1948 (Fed. Cir. 1999).

angiogenesis" by using the recited "agent that interferes with specific binding of the α5β1 integrin" because the prior art **did not know** that α5β1 integrin expression was associated with angiogenesis, and because the instant Specification is the **first** report of such an association.[83] The Examiner responded that Pasqualini *et al.*'s "agent [*i.e.*, sFN] was *known* to be a ligand for alpha 5 beta 1 integrin and was specifically shown to inhibit angiogenesis."[84] However, the Examiner does not pose the proper inquiry.[85] The question is not whether each of these properties of sFN was disclosed by the prior art, but whether the art taught a **nexus** between these properties such that one of skill in the art would be motivated to **combine** them as recited in the claims. The Examiner's argument lacks the logical thread of explaining how a nexus between two properties can be established in the face of the art's ignorance of the existence of one of the properties (*i.e.*, that α5β1 plays a role in angiogenesis). The Examiner has fallen victim to the insidious effect of **impermissible hindsight** wherein that which only the inventor taught is used against its teacher.[86]

With respect to the previously rejected Claims 1-5, 9-13, 19, 20, 55-72, and 75, Applicant also previously argued that it is improper for the Examiner to establish obviousness by relying on the alleged inherency of the recited limitations in Pasqualini *et al.*'s sFN because **inherency has no place in an obviousness analysis.**[87] The Federal Circuit has unequivocally stated that:

---

[83] Applicant notes that this argument is equally applicable to the newly rejected Claims 80-106, 108-117, 119 and 120 since they recite the same limitations as the previously rejected Claims 1-5, 9-13, 19, 20, 55-72, and 75.

[84] (Emphasis added) Office Action, page 13, lines 6-10.

[85] Applicant's argument is made without acquiescing to the Examiner's unsupported statement.

[86] See, for example, *In re Dembiczak,* 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999).

[87] Applicant notes that this argument is equally applicable to the newly rejected Claims 80-106, 108-117, 119 and 120 since they recite the same limitations as the previously rejected Claims 1-5, 9-13, 19, 20, 55-72, and 75.

> "Inherency and obviousness are distinct concepts."[88] "[A] retrospective view of inherency is *not* a substitute for some teaching or suggestion supporting an obviousness rejection."[89] "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."[90]

The Examiner continued to ignore this legal principle by insisting on applying the alleged inherency of the claims' limitations in Pasqualini *et al.* Because the Examiner's assertion of motivation to combine the references relies on a legally inappropriate standard, this assertion is improper.

Applicant also previously argued that Pasqualini *et al.*'s disclosure of topical administration of sFN is **irrelevant** to rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75 because (1) none of these claims recites administration of the agent using eye drops,[91] and (2) this disclosure does not add to the **deficient motivation** for reducing or inhibiting angiogenesis.[92] The Examiner did not respond to the first argument, so its validity stands uncontested. The Examiner responded to the second argument by asserting that "for the reasons previously set forth, both the motivation and the mode of administration are obvious."[93] Applicant reiterates that motivation is lacking because the prior art **did not know** that $\alpha 5\beta 1$ integrin expression was associated with angiogenesis, and because inherency is **not a substitute** for motivation.

---

[88] *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

[89] (Emphasis added) *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

[90] *In re Newell*, 891 F.2d 899, 901,13 USPQ2d 1248, 1250 (Fed. Cir.1989).

[91] Only rejected Claim 70 recites administration of eye drops.

[92] Applicant notes that this argument is equally applicable to the newly rejected Claims 80-106, 108-117, 119 and 120 since they recite the same limitations as the previously rejected Claims 1-5, 9-13, 19, 20, 55-69, 71, 72, and 75.

[93] Office Action, page 13, lines 10-11.

The Examiner mis-characterized Applicant's prior arguments as stating that "none of the claims recite cytotoxin-linked agents,"[94] and "suggested that Applicant read claims 19, 20."[95] The Examiner is invited to point out where this alleged argument was made in Applicant's prior response since Applicant nowhere stated that "none of the claims recite cytotoxin-linked agents." Rather, Applicant did not include Claims 19 and 20 in its prior argument that Pasqualini *et al.*'s disclosure of cytotoxin-linked agents is **irrelevant** to the previously rejected Claims 1-5, 9-14, 55-72, and 75 (and to the newly rejected Claims 80-106, and 110-117) because none of **these** claims recites cytotoxin-linked agents.[96] The Examiner did not comment on this argument, so its validity is conceded.

Applicant further previously argued that, as to each of the previously rejected Claims 1-5, 9-13, 19, 20, 55-72, and 75,[97] Pasqualini *et al.*'s disclosure of cytotoxin-linked agents adds nothing to the reference's **inadequate motivation** for reducing or inhibiting angiogenesis by interfering with $\alpha 5\beta 1$'s binding to an integrin, as explained above. The Examiner did not respond to this argument. Accordingly, it stands un-rebutted.

The Examiner misapprehended yet another of Applicant's prior arguments as stating that "none of the claims recite injecting agents directly into a tumor"[98] and "suggested that Applicant read claim 67."[99] The Examiner is respectfully requested to indicate where Applicant's prior response made this alleged argument since it does not appear anywhere in the prior response. What Applicant **did** argue was that alleged motivation to inject the agents directly into Pasqualini *et al.*'s or Ruoslahti *et al.*'s tumors is **irrelevant** to any of the previously rejected Claims 1-5, 9-14, 19, 20, 55-66, 68-72, and 75, (and of the newly rejected Claims 80-106, 108-117, 119, and 120) because none of **these** claims recites injecting the

---

[94] Office Action, page 12, fourth paragraph.

[95] Office Action, page 13, first paragraph.

[96] Only rejected Claims 19, 20, 108, 109, 119, and 120 recite an agent linked to a cytotoxin.

[97] Applicant's prior argument is equally applicable to the newly rejected Claims 80-106, 108-117, 119, and 120.

[98] Office Action, page 12, fourth paragraph.

[99] Office Action, page 13, first paragraph.

agent.[100] Claim 67 was not mentioned by Applicant. The Examiner was silent on this argument, thus conceding its validity.

Applicant also previously argued that with respect to each of the previously rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75 (and newly rejected Claims 80-106, 108-117, 119, and 120) an alleged motivation to inject an agent directly into a tumor fails to supplement the **insufficient motivation** for reducing or inhibiting angiogenesis by interfering with $\alpha 5\beta 1$'s binding to an integrin, as explained above. Since the Examiner did not rebut this argument.

In view of the above, a motivation to combine the teachings of the references to arrive at the claimed invention continues to be lacking. This alone negates a *prima facie* case of obviousness.

3. A Reasonable Expectation Of Success Is Not Established

A fundamental requisite of establishing a *prima facie* case of obviousness is that there is a reasonable expectation of success in practicing the recited method steps.

> "[T]he reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."[101]

The Examiner's singular statement with regard to this prong of a *prima facie* case of obviousness is that "given the teaching in Pasqualini et al. and the specific exemplification of inhibition of angiogenesis in Pasqualini, one would have a reasonable expectation of success."[102] This conclusory statement is nothing more than a naked assertion which is unsupported by scientific reasoning or evidence. This evidentiary omission precludes establishing a *prima facie* case of obviousness, and entitles Applicant to withdrawal of the rejection.

Applicant previously argued that any alleged expectation of success is **rebutted** by the prior art's (including the cited references') **ignorance** of a role for $\alpha 5\beta 1$ integrin in

---

[100] Only rejected Claim 67 recites administering an agent into neoplasm. However, such administering is not limited to "injecting" into a neoplasm.

[101] *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) as cited in *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

[102] Office Action, page 13, first paragraph, last sentence.

angiogenesis; this role was first discovered and disclosed by Applicant in the instant Specification. The Examiner is again respectfully reminded that the reasonable expectation of success must be founded in the prior art, not Applicant's disclosure. In view of the prior art's ignorance of α5β1's role in angiogenesis, no logical argument can be advanced in support of the cited references' teaching of a reasonable expectation of success in inhibiting angiogenesis by using an agent which acts by the **hitherto unknown mechanism** of inhibiting the specific binding of α5β1 integrin to a ligand. The Examiner did not comment on this argument. Accordingly, its correctness is unrebutted.

Applicant also previously argued that it is improper to rely on alleged inherency to establish a reasonable expectation of success in practicing the recited steps because

> "Inherency and obviousness are distinct concepts."[103] "That which may be inherent is not necessarily known. Obviousness *cannot* be predicated on what is *unknown*."[104]

Because the Examiner did not dispute that α5β1's role in angiogenesis was unknown, and because obviousness cannot be predicated on what is unknown, it is inescapable that this prong of a *prima facie* case of obviousness cannot be made. This argument stands un-rebutted by the Examiner's silence.

Applicant further reiterates its prior argument that even if inherency were improperly resorted to, inherency is anyway lacking as discussed *supra*.

Because, not one, but each of the **three** elements of a *prima facie* case of obviousness remains lacking, a *prima facie* case of obviousness cannot be established. It is therefore respectfully requested that the rejection of Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, and 120 under 35 U.S.C. § 103(a) for alleged obviousness be withdrawn.

---

[103] *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

[104] (Emphasis added) *In re Newell*, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir.1989).

B. Applicant's Evidence Rebuts Obviousness

Even assuming, *arguendo*, that a *prima facie* case of obviousness is made, Applicant's following evidence rebuts both the motivation to combine the references as well a reasonable expectation of success when practicing the combination.

With respect to motivation to combine the teachings of Pasqualini *et al.* with any other reference, this is rebutted by the prior art which shows that Pasqualini *et al.* **teaches away** from the claimed combination. The law clearly states that:

"A teaching away alone can defeat obviousness."[105]

Yi *et al.*[106] **teaches away** from the claimed invention because (as discussed *supra*) it proposes that sFN acts either by accelerating removal of tumor cells from the circulation, or by binding to $\alpha v\beta 3$ integrin. Because these mechanisms point the artisan in a direction which is different from the recited interference with $\alpha 5\beta 1$ binding, they dissuade the artisan from following the route carved by Applicant.

Morla *et al.*[107] also **teaches away** from the claimed methods because Morla *et al.* demonstrates that the biological effects of Pasqualini *et al.*'s sFN may be mediated by receptors other than $\alpha 5\beta 1$. It states:

> "the superadhesiveness of cells on [superfibronectin] may be due to binding of the cells through more than one class of receptors: integrins and a family of receptors not related to the integrins. This is in *sharp contrast* to the binding of cells to regular fibronectin, which is mediated entirely by integrins."[108]

Morla *et al.*'s above teaching defeats motivation to combine Pasqualini *et al.* with any other reference because it teaches the artisan that several receptors, rather than $\alpha 5\beta 1$, mediate the function of sFN.

---

[105] *Winner International Royalty Corp. v. Wang*, 53 USPQ2d 1580, 202 F.3d 1340, 13449 (Fed. Cir. 2000), citing *Gambro Lundia AB v. Baxter Healthcare Crop.*, 110 F.3d 1573, 1579, 42 USPQ2d 1378, 1383 (Fed. Cir. 1997).

[106] Yi *et al.* (2001); Tab 1.

[107] Morla *et al.* (1994), Tab 3.

[108] (Emphasis added) Morla *et al.*, paragraph bridging pages 195 and 196.

Varner *et al.*[109] (discussed *supra*) also corroborates Morla *et al.*'s **teaching away** from practicing the claimed steps because it also demonstrates that Pasqualini et al.'s sFN interacts with receptors other than $\alpha5\beta1$.

Ruoslahti *et al.* further validates Varner *et al.*'s and Morla *et al.*'s **teaching away** from the claimed methods because it teaches that peptides which inhibit binding of $\alpha5\beta1$ to a ligand function by inhibiting the **attachment** of **tumor cells** to fibronectin,[110] rather than by the recited reduction of **angiogenesis** by **endothelial cells**. Since the Examiner took the position that sFN is a peptide,[111] then the artisan would be motivated to assume that the mode of action of Pasqualini *et al.*'s sFN would be the same as that of Ruoslahti *et al.*'s peptides. Thus, the artisan would be motivated to believe that Pasqualini *et al.*'s sFN functions by inhibiting **cell attachment** by **tumor cells** rather than reducing **angiogenesis** by endothelial cells. Accordingly, this motivation directs the artisan towards interfering with tumor cell attachment rather than towards the recited reduction of "angiogenesis" by endothelial cells. This is a teaching away from the claimed methods which further negates obviousness.

Additionally, the combination of Pasqualini *et al.* and Kim *et al.*[112] provides a "teaching away" from considering Pasqualini *et al.*'s sFN as the recited "agent" because they show that sFN is **functionally different** from agents which interfere with specific binding of $\alpha5\beta1$ to a ligand. Specifically, Pasqualini *et al.* demonstrates that sFN suppresses cell migration on both fibronectin **and** collagen,[113] whereas Kim *et al.* teaches that agents which inhibit specific binding of $\alpha5\beta1$ to fibronectin inhibit cell attachment and migration to **only** fibronectin, not to collagen.[114] Because of this functional difference, the artisan would not be

---

[109] Varner *et al.* (1995), Tab 2.

[110] Ruoslahti *et al.*, Figures 5 and 11; page 5, lines 24-25; page 6, fifth paragraph; page 31, lines 11-34; and page 32, lines 1-8.

[111] Office Action, page 6, lines 7-10.

[112] Kim *et al.* (2000), Tab 4.

[113] Pasqualini *et al.*, column 3, lines 17-22; and Figure 7.

[114] Kim *et al.*, page 1353, paragraph bridging columns 1 and 2; and Figure 4D.

impelled to consider that Pasqualini *et al.*'s sFN functions as "an agent that interferes with specific binding of the α5β1 integrin to a ligand."

With respect to a reasonable expectation of success in inhibiting angiogenesis by the step of interfering with the binding of α5β1 to a ligand, this is rebutted by Yi *et al.* Because Yi *et al.* teaches that sFN acts by impacting either tumor cells or αvβ3 integrin on endothelial cells, one skilled in the art would not have any scientific basis to predict that the antiangiogenic effect of sFN is mediated by sFN's interference with **any** target (much less with the recited α5β1 binding) other than tumor cells or αvβ3.

Morla *et al.* also contradicts an alleged expectation of success. In particular, the artisan is taught by Morla *et al.* that the biological effects of sFN may be mediated via any one of **several** receptors. Nothing in the prior art reasonably predicts for the artisan that the recited α5β1 is **the receptor**, among several alternative possibilities, with causes Pasqualini *et al.*'s inhibition of angiogenesis by sFN. This is especially so in view of the prior art's ignorance of α5β1's role in angiogenesis. Thus, Morla *et al.* shows that if the artisan arguably were to select α5β1, they would **not** have a **reasonable basis for predicting** that this particular receptor, from among the several other possible receptors, would be the one which mediates sFN's function in inhibiting angiogenesis.

Ruoslahti *et al.* further refutes a reasonable expectation of success. Based on the above-discussed teaching of Ruoslahti *et al.*, this reference encourages the artisan to expect that Pasqualini *et al.*'s sFN functions by inhibiting **cell attachment** by **tumor cells** and not by another mechanism. Thus, the artisan would not reasonably expect that interference with a mechanism that is different from tumor cell attachment (*i.e.*, the recited reduction of angiogenesis) would account for sFN's effects.

A reasonable expectation of success is also rebutted by Pasqualini *et al.* and Kim *et al.* because, as discussed *supra*, these references demonstrate that sFN **functions differently** from agents that interfere with the binding of α5β1 to a ligand. In view of this **functional difference**, the artisan's reasonable expectation would be that, similarly to its different effect on cell migration on collagen, sFN would also have a different effect on angiogenesis from the recited "agent." Conversely, the artisan would **not** have a **reasonable basis for predicting** that sFN would have a **similar** effect (*i.e.*, reducing angiogenesis) as that caused by the recited "agent."

Because the evidence rebuts both a motivation to combine the references and a reasonable expectation of success in practicing the combination, a *prima facie* case of obviousness (if arguably made) is rebutted. Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, and 120 under 35 U.S.C. § 103(a) for alleged obviousness.

6. Rejection Of Claims 1-5, 9-14, 19, 20, 55-72, 75, And 80-120 Under 35 U.S.C. §103(a) Over Pasqualini *et al.* In View Of Ruoslahti *et al.*

Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 stand newly rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714).[115] Applicant cannot agree because a *prima facie* case of obviousness is not made, and is rebutted by Applicant's evidence.

A. A *prima facie* Case Of Obviousness Is Not Made

The Examiner has failed to establish **each of the three** requirements of a *prima facie* case of obviousness as discussed below.

1. The Combined References Do Not Disclose All The Limitations Of The Claims

The Examiner argued that Pasqualini *et al.* uses a SEQ ID NO:18,[116] and that Ruoslahti *et al.* discloses that its SEQ ID NO:12 which contains Pasqualini *et al.*'s SEQ ID NO:18 "allows the *specific* isolation of alpha 5 beta 1 integrin."[117] Importantly, however, this disclosure does **not** teach that the alleged specificity of binding of these peptides to $\alpha 5\beta 1$ causes the recited "reducing or inhibiting angiogenesis." To the contrary, as discussed *supra*, Ruoslahti *et al.* expressly teaches that its peptides function by inhibiting **attachment** of **tumor cells** to fibronectin, instead of inhibiting **angiogenesis** by **endothelial cells**. Thus, the element of "reducing or inhibiting angiogenesis" is lacking.

---

[115] Office Action, page 13, item 9.

[116] Office Action, paragraph bridging pages 14 and 15.

[117] (Emphasis added) Office Action, page 15, first paragraph, citing Ruoslahti *et al.*, page 17, lines 8-10.

2. Motivation Is Absent

The Examiner argued that there is motivation to "substitute SEQ ID NO:12 of . . . [Ruoslahti *et al.*] or SEQ ID NO:18 of . . . [Pasqualini *et al.*] for the sFN of . . . Pasqualini *et al.*] because . . . [Ruoslahti *et al.*] specifically teaches that peptides of the invention compete *in vivo* for the *binding* of integrin." This argument ignores the fact that "reducing or inhibiting angiogenesis" is an element of the claimed invention. In other words, in order for the Examiner to establish the requisite motivation, she must

> "show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with *no knowledge* of the *claimed invention*, would select the elements [of reducing or inhibiting angiogenesis] from the cited prior art references for combination in the manner claimed."[118]

However, this has not been done. In fact, motivation **cannot** be done with "no knowledge" of whether the peptides of Ruoslahti *et al.* cause "reducing or inhibiting angiogenesis." Applicant respectfully reminds the Examiner that Ruoslahti *et al.* and Pasqualini *et al.* **did not know** that the peptides which they used caused a reduction or inhibition of angiogenesis. Rather, Applicant's invention was the first teaching of such a nexus. The Examiner is invited to point out, with specificity, where either Pasqualini *et al.* or Ruoslahti *et al.* teaches a causative connection between using their peptides and "reducing or inhibiting angiogenesis."

In view of the prior art's **ignorance** of this recited limitation, and since the Examiner is prohibited from using what is **unknown** to the art for the purpose of establishing motivation,[119] this prong of a *prima facie* case of obviousness must fail, necessitating withdrawal of the rejection for alleged obviousness.

3. A Reasonable Expectation Of Success Remains Unestablished

One of the requisites of establishing a *prima facie* case of obviousness is that the **cited references** (not Applicant's disclosure) teach a reasonable expectation of success in practicing

---

[118] (Emphasis added) *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *Robotic Vision Systems Inc. v. View Engineering Inc.*, 51 USPQ2d 1948 (Fed. Cir. 1999).

[119] Applicant also incorporates by reference its above argument that inherency cannot be used to establish obviousness.

the recited method steps.[120] The Examiner argued that "one of ordinary skill in the art would have expected to successfully *inhibit angiogenesis* and treat pathologies with angioproliferative components by administering the *peptide*."[121] This alleged expectation is unsupported. Indeed, it is contradicted by the cited prior art's **ignorance** of a role for α5β1 integrin in angiogenesis, let alone that the peptides of Pasqualini *et al.* or Ruoslahti *et al.* function by "reducing or inhibiting angiogenesis."[122] Thus, the third prong of a *prima facie* case of obviousness is absent.

Because each of the **three** elements of a *prima facie* case of obviousness is unestablished, a *prima facie* case of obviousness cannot be made. Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 under 35 U.S.C. § 103(a) for alleged obviousness.

B. Applicant's Evidence Rebuts Obviousness

Even if a *prima facie* case of obviousness were arguably established (which it was not), it is rebutted by Ruoslahti *et al.* for the reasons discussed *supra*. In particular, Ruoslahti *et al.* negates motivation to combine its disclosure with that of Pasqualini *et al.* because it teaches that peptides which inhibit binding α5β1 to a ligand function by inhibiting the **attachment** of **tumor cells** to fibronectin,[123] rather than by the recited reduction of **angiogenesis** by **endothelial cells**. This motivates the artisan to use the peptides to interfere with tumor cell attachment to fibronectin, and **away** from the recited reduction of "angiogenesis" by endothelial cells.

Ruoslahti *et al.* also refutes a reasonable expectation of success because it directs the skilled in the art to **expect** that its (and Pasqualini *et al.*'s) peptides function by inhibiting **cell**

---

[120] *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) as cited in *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

[121] Office Action, page 15, last full sentence.

[122] Applicant also incorporates by reference its above argument that inherency cannot be used to establish obviousness.

[123] Ruoslahti *et al.*, Figures 5 and 11; page 5, lines 24-25; page 6, fifth paragraph; page 31, lines 11-34; and page 32, lines 1-8.

attachment by **tumor cells** and not by another mechanism, including the recited mechanism of reducing angiogenesis.

Because Ruoslahti *et al.* contradicts the motivation to combine the references as well as a reasonable expectation of success in practicing the combination, a *prima facie* case of obviousness (if arguably made) is rebutted. Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, and 120 under 35 U.S.C. § 103(a) for alleged obviousness.

7. Rejection Of Claims 80-86, 90-96, And 110-116 Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 80-86, 90-96, and 110-116 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description.[124] In particular, the Examiner contended that support is lacking for "the limitation of an agent wherein binding of said agent to alpha 5 beta 1 integrin is at least two-fold, five-fold, ten fold greater than the binding of said agent to an integrin other than alpha 5 beta 1" because "the support is drawn only to *peptides* and not to the broadly claimed '*agent.*'"[125] Applicant respectfully must disagree because the Specification provides adequate support as evidenced by the enclosed Declaration by Dr. Woods.

The fundamental factual inquiry on whether the written description requirement is satisfied is whether the specification:

> "convey[s] with reasonable clarity to *those skilled in the art* that, as of the filing date sought, he or she was in possession of the invention."[126]

Dr. Woods, who is skilled in the art[127] addressed the Specification's teachings[128] and concluded therefrom "that the inventor contemplated that this desirable property (*i.e.*, relative

---

[124] Office Action, page 16, item 10.

[125] (Emphasis added) Office Action, page 16, item 10.

[126] (Emphasis added) *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996), citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

[127] Declaration by Dr. Woods, item 1.

[128] Declaration by Dr. Woods, items 6 and 7.

binding to α5β1 as compared to αVβ3) which makes the exemplary antibodies and peptides 'useful' in the claimed methods, is also a desirable property that is contemplated for **any other type of agent**, including the third exemplary type of nonpeptide small organic molecule. In other words, the Specification conveys to me that the inventor contemplated that one desirable property of **any agent** that interferes with the specific binding of α5β1 integrin to its ligand is that the agent (regardless of its type) binds with at least about a two-fold greater, at least about five-fold greater, or at least about ten-fold greater specificity for α5β1 than for αVβ3."[129]

In view of Dr. Woods's Declaration, the Specification conveys to the artisan that the inventor was in possession of the recited binding ranges with respect to the recited agent. Accordingly, the rejection of Claims 80-86, 90-96, and 110-116 under 35 U.S.C. §112, first paragraph, is in error, and should be withdrawn.

8. Rejection Of Claims 86, 96, And 116 Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 86, 96, and 116 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description.[130] The Examiner argued that "there is nothing in the suggested support drawn to an agent which does not interfere with the *specific binding* of a ligand to any integrin since the support is only drawn to *fold-affinity*."[131]

Applicant respectfully must traverse because the enclosed Declaration by Dr. Woods demonstrates that the Specification clearly conveys to the artisan that the inventor contemplated the recited limitations. In particular, based on the Specification's teachings, Dr. Woods, who is skilled in the art,[132] concluded that although the Specification's "teaching refers to a desirable property of an antibody,[133] it is nonetheless my opinion that this desirable

---

[129] Declaration by Dr. Woods, item 7.

[130] Office Action, page 16, litem 11.

[131] (Emphasis added) Office Action, page 17, first paragraph.

[132] Declaration by Dr. Woods, item 1.

[133] The desirable property is "that the antibody does not interfere with the *specific binding* of a ligand." (Emphasis added) Declaration by Dr. Woods, item 9.

property was contemplated by the inventor to apply to **any agent** because the Specification teaches that antibodies are an example of an agent."[134]

Because Dr. Woods's Declaration shows that the Specification conveys to the artisan that the inventor was in possession of the recited "specific binding" with respect to the recited "agent," it is respectfully requested that the rejection of Claims 86, 96, and 116 under 35 U.S.C. §112, first paragraph, be withdrawn.

9. Rejection Of Claims 80-120 Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 80-120 stand rejected under 35 U.S.C. §112, first paragraph, for alleged non-enablement.[135] Applicant respectfully must traverse. The test of enablement is:

> "whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[136]

Applicant submits that enablement is satisfied because of the Examiner's admission and her failure to establish the need for undue experimentation, and because enablement is supported by the Specification and the prior art.

A. Enablement Is Admitted By The Examiner

The Examiner is respectfully reminded that if a claim is enabled, then claims depending therefrom are also enabled.[137] The Examiner found that the Specification is "enabling for an agent that specifically binds to alpha 5 beta 1 integrin."[138] This **admits** enablement of each of Claims 1-5, 9-14, 19, 20, 55-72, and 75 which recite this limitation,

---

[134] Declaration by Dr. Woods, item 9.

[136] MPEP 2164.01, citing *United States v. Electronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976).

[137] *Sheller-Globe Corp. v. Milsco Manufacturing, Co.*, 206 USPQ 42, 64 (U.S. District Court For the Eastern District of Wisconsin 1979) (Non-enablement of independent claims results in non-enablement of claims dependent therefrom).

[138] Office Action, page 17, last full paragraph.

without regard to the degree of binding of the agent to $\alpha 5\beta 1$ integrin as compared to another integrin. Indeed, none of these claims was rejected for non-enablement. Since each of the **rejected** Claims 80-120 depends directly or indirectly from the **admittedly enabled** Claims 1, 10, 12, 55, and 57, then the law stipulates that rejected Claims 80-120 are necessarily enabled. This, without more, necessitates withdrawal of the rejection of Claims 80-120 for non-enablement.

B. Non-Enablement Is Not Established, And Is Rebutted By The Specification's Methods

The Examiner argued that the Specification "does not reasonably provide enablement for an agent that binds to [*sic.*] alpha 5-beta 1 two fold, five fold or ten fold greater than any other integrin"[139] and premised this argument on averring that "the specification does not define *selective binding* or define *specific binding* in limiting terms, that is in terms of fold-affinity."[140] Based on this premise, the Examiner found that the meaning of these terms must be borrowed from the prior art of Ruoslahti *et al.* and "it is assumed for examination purposes that the art recognized definition of WO95/14714 is the art recognized definition of the term, that is that 'selective binding' refers to a 10-fold higher affinity for one integrin as compared to another and that 'specific binding' refers to 100-fold high affinity for one integrin as compared to another."[141]

The Examiner's resort to the art's definition of the term "selective binding" is **irrelevant** because this term is **not recited** in **any** of the claims.

As to the term "specific binding" which **is** recited by the claims, the Examiner's premise with respect to this term is legally unsound for two reasons. In the first instance, the law does not require numerical limits for clarity of a claim term.

---

[139] *Id.*

[140] (Emphasis added) Office Action, sentence bridging pages 17-18.

[141] Office Action, page 18, first paragraph, citing Ruoslahti *et al.*, page 12, lines 18-30.

> "Mathematical precision should not be imposed for its own sake; a patentee has the right to claim the invention in terms that would be understood by persons of skill in the field of the invention."[142]

Thus, the Examiner's apparent requirement for a definition of the term "specific binding" which includes "fold-affinity" is contrary to the law because the Specification's express definition of this term does not include numerical limitations.

Secondly, the Examiner impermissibly uses a prior art definition which is contrary to Applicant's express definition. The term "specific binding" is qualitatively defined by the Specification as follows:

> "As used herein, the term 'specific binding' or 'binds specifically,' when used in reference to the interaction of two or more molecules, means that the molecules can associate with each other under *in vivo* conditions and *in vitro* conditions when incubated under appropriate conditions, which can mimic *in vivo* conditions."[143]

In other words, the Specification qualitatively defines "specific binding" based on the ability of two molecules to associate **without regard** to the quantitative degree of association. The plain meaning of this qualitative definition is clear to the artisan, without resort to numerical ranges. It is **impermissible** for the Examiner to ignore Applicant's **express definition** of this term in favor of another alleged definition by Ruoslahti *et al.* Under the law, applicants are their own lexicographers and can define in the claims what they regard as their invention essentially in "whatever terms they choose."[144] Because, Applicant has expressly defined the recited "specific binding" in **qualitative** rather than quantitative terms, the **numerical** values which Ruoslahti *et al.* ascribe to their use of this term is **irrelevant**, and cannot be imputed to the instant claims.

Because the Examiner's premise is legally and factually unsound, it cannot be used to support her arguments of non-enablement. For this reason, the Examiner's arguments of non-enablement will be considered *infra* without regard to Ruoslahti *et al.*'s definition of the recited term "specific binding."

---

[142] *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1557, 37 USPQ2d 1609 (Fed. Cir.), *cert. denied*, 518 U.S. 1005 (1996).

[143] Specification, page 18, lines 15-20.

[144] MPEP 2173.01, citing *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971).

The Examiner argued that the "specification provides *insufficient guidance* with regard to these issues [of sequestration of the agent by targets other than $\alpha 5\beta 1$, the agent's variable stability, half-life or clearance from the blood, the agent's inability to penetrate tissues or cells, and its insufficient local concentration] and provides no working examples . . . and no evidence has been provided which would allow one of skill in the art to *predict the efficacy of the claimed methods with a reasonable expectation of success.*"[145] The Examiner is respectfully reminded that the test of enablement is not whether there is a teaching or evidence which allows the artisan to "predict the efficacy of the claimed methods with a reasonable expectation of success." Rather, the test of enablement is:

> "whether one skilled in the art *could make or use* the *claimed invention* from the disclosures in the patent coupled with information known in the art without undue experimentation."[146] "[T]he key word is 'undue' not 'experimentation.'"[147]

Importantly, the enablement inquiry addresses what is recited by the **claimed invention**. What is recited is indeed enabled. In particular, each of the rejected Claims 80-120 recites that the agent acts by "reducing or inhibiting angiogenesis." With respect to this limitation, the proper inquiry is whether there are methods available to the artisan (from the Specification and/or the prior art) which enable him to determine whether angiogenesis is reduced or inhibited. The answer must be in the affirmative in view of both the Specification's and prior art's teachings. For example, the Specification teaches that the level of angiogenesis may be determined for any agent by, for example, counting the number of blood vessel branch points in the art-accepted *in vivo* chick chorioallantoic membrane (CAM) angiogenesis assay,[148] or determining the number of human CD31 positive blood vessels in human-derived tissue which is transplanted into an animal host.[149] The prior art also teaches that the level of angiogenesis

---

[145] Office Action, sentence bridging pages 19 and 20.

[146] MPEP 2164.01, citing *United States v. Electronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976).

[147] *In re Wands*, 8 USPQ2d 1404, citing *In re Angstadt*, 537 F.2d at 504, 190 USPQ at 219.

[148] Specification, item 3 beginning on page 41, line 26, through page 43, line 13.

[149] Specification, Example III, pages 50-51.

may be determined using an *in vitro* tubular cord formation assay which shows growth of new blood vessels at the cellular level [D. S. Grant *et al.*, Cell, 58:933-943 (1989)].[150] In view of the Specification's and prior art's teaching of routine methods to determine the level of angiogenesis in a tissue, the recited element of "reducing or inhibiting angiogenesis" is enabled.

The claimed invention in rejected Claims 86-89, 96-109, and 116-120 also recites that the agent interferes with "specific binding of the α5β1 integrin to a ligand." Since the "specific binding" is defined by the Specification to refer to the ability of two molecules to "associate with each other under *in vivo* conditions and *in vitro* conditions,"[151] then the proper inquiry is whether the Specification and/or prior art teach methods to determine whether or not such association has occured. This is indeed the case because the Specification also teaches that the α5β1 integrin receptor ligand binding assay may be used to determine the association between α5β1 integrin and a ligand.[152] Since the artisan has within his disposal a routine assay for this limitation, this limitation is enabled.

The claimed invention also recites that the binding of the agent to α5β1 is at least two-fold,[153] five-fold,[154] or ten-fold[155] greater than that to another ligand. The Specification teaches that the integrin receptor ligand binding assay may be used to quantitatively determine the level of association of the agent to α5β1 and to any other integrin.[156] In view of the availability of this routine assay, this limitation is enabled.

In sum, because the above analysis under the proper inquiry demonstrates enablement of each of the **individually** recited limitations, the **combination** of these limitations in the claims is deemed enabled.

---

[150] A copy of this reference will be provided if so requested by the Examiner.

[151] Specification, page 18, lines 15-20.

[152] Specification, item 4, beginning on page 43, through page 44, line 3.

[153] Claims 80, 81, 90, 91, 110, and 111.

[154] Claims 82, 83, 92, 93, 112, and 113.

[155] Claims 84, 85, 94, 95, 114, and 115.

[156] Specification, item 4, beginning on page 43, through page 44, line 3.

Applicant notes that although the Examiner **admitted** that agents which bind to α5β1 integrin with **at least** 100-fold affinity are **enabled,**[157] she nonetheless, alleged non-enablement of agents which bind to α5β1 integrin with **less than** 100-fold greater affinity to α5β1 than to another integrin. At best, this ground of rejection can arguably be directed at only Claims 80-85, 90-95, 110,-115 which recites the relative fold binding of the agent to α5β1 as compared to another ligand. Additionally, even if (for the sake of argument) agents with **less than** 100-fold greater affinity to α5β1 than to another integrin did not result in the recited reduction of angiogenesis, this would not negate enablement. The law says:

> "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'it is not a function of the claims to specifically exclude . . . possible inoperative substances."[158]

Accordingly, it is of no moment to enablement that the Examiner speculates that some agents may be inoperative. Because, each of Claims 80-85, 90-95, 110,-115 includes within its scope agents which bind with at least 100-fold affinity, and which the Examiner **admitted** were enabled, these claims are *ipso facto* enabled.

The Examiner indicated that "variables such as biological stability, half-life or clearance from the blood are important parameters in achieving *successful therapy.*"[159] But "successful therapy" is irrelevant because it is **not recited** in the rejected claims. What **is** recited is that the agent reduces angiogenesis. Since **this** is enabled by the above-discussed routine methods, the variables referred to by the Examiner are immaterial.[160]

---

[157] The Examiner's contention that "it is clear that there is neither guidance on nor exemplification of any 'agent' that does **not** have at least 100 fold binding to alpha 5 beta 1 integrin" (Office Action, page 19, second paragraph) is an admission that agents which **do** have 100 fold greater binding to α5β1 than to another integrin **are enabled**.

[158] *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.,* 750 F.2d 1569, 1576, 224 USPQ 409 (Fed. Cir. 1984).

[159] Office Action, middle of page 19.

[160] Applicant's argument is equally applicable to the other variables discussed by the Examiner, namely, sequestration of the agent by targets other than α5β1, the agent's inability to penetrate tissues or cells, and its insufficient local concentration. Office Action, page 19, last paragraph.

Because the Specification coupled with information known in the art provides the artisan with routine methods for using each of the recited limitations, there can be no "undue" experimentation. Accordingly Claims 80-120 are enabled.

C. Additional Evidence Supporting Enablement

Kim *et al.* (Tab 4) rebuts the Examiner's contention of non-enablement by further demonstrating that the Specification's routine methods may be used to determine the level of angiogenesis in a tissue in response to administration of an agent which interferes with the specific binding of α5β1 integrin, **regardless** of the level of this interference. In particular, using methods disclosed in the instant Specification,[161] Kim *et al.* demonstrates inhibition of angiogenesis *in vivo* in both a chick chorioallantoic membrane (CAM) angiogenesis assay, and a SCID mouse assay by using as "agents" a monoclonal anti-α5β1 antibody, the CRETAWAC peptide, and the non-peptide small molecule SJ749. For example, Kim *et al.* shows that in the CAM assay, (1) anti-α5β1 antibody inhibits angiogenesis as determined visually,[162] by immunohistochemistry,[163] and by quantitation of the number of blood vessel branch points;[164] and (2) the CRETAWAC peptide[165] and the molecule SJ749 inhibit angiogenesis as determined by the number of blood vessel branch points.[166] Using a different *in vivo* assay in which SCID mice are engrafted with human neonatal foreskin, Kim *et al.* shows that anti-α5β1 antibody inhibits angiogenesis in the human tissue as quantitated by the number of $CD31^+$ cells.[167] Because Kim *et al.*'s methods are routine, are the same as the Specification's

---

[161] The Specification discloses experimental details of the chick chorioallantoic membranae angiogenesis assay (page 41, line 26 - page 43, line 13; page 51, line 21 - page 53, line 26), and the SCID mouse assay (page 50, line 6 - page 51, line 18).

[162] Kim *et al.*, Figures 5A and 8A.

[163] Kim *et al.*, Figure 8H-I.

[164] Kim *et al.*, Figures 5B, 5E, 8B, and 8G.

[165] Kim *et al.*, Figures 5C and 5F.

[166] Kim *et al.*, Figures 5D and 5F.

[167] Kim *et al.*, Figures 6A and 6B.

methods, and can detect the level of angiogenesis in a tissue regardless of the binding specificity of the "agent" to α5β1 integrin, Kim *et al.* rebuts any alleged need for undue experimentation.

Pasqualini *et al.* also rebuts the Examiner's contention that variables associated with the agent point to non-enablement. This is because the same "variables" (such as the agent's biological stability, half-life or clearance from the blood, sequestration of the agent by targets other than α5β1, the agent's inability to penetrate tissues or cells, and its insufficient local concentration) are implicated in Pasqualini *et al.*'s use of sFN to inhibit cancer, and yet Pasqualini *et al.*'s claims which are directed to using sFN to inhibit cancer are **enabled**. In particular, Applicant notes that Pasqualini *et al.*'s Claim 1 is directed to a "method of inhibiting cancer in a subject, comprising administering superfibronectin to the subject, in an amount effective to inhibit cancer in the subject." Because issued U.S. patent claims are presumptively enabled, Pasqualini *et al.*'s Claim 1 is enabled. This is the case notwithstanding that similar "variables" apply to Pasqualini *et al.*'s use of sFN to inhibit cancer as to the instant invention's use of an agent to reduce angiogenesis. Accordingly, Pasqualini *et al.* further demonstrates that enablement is not negatived by the alleged "variables."

In view of the above, Applicant requests that the rejection of Claims 80-120 under 35 U.S.C. §112, first paragraph, for alleged non-enablement be withdrawn.

CONCLUSION

All grounds of rejection and objection of the Office Action of November 16, 2001 having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (415) 904-6500.

Dated: February 19, 2002

Kamrin T. MacKnight
Registration No. 38,230
101 Howard Street, Suite 350
San Francisco, California 94105
415.904.6500

APPENDIX I
MARKED-UP VERSION OF SPECIFICATION'S REPLACEMENT PARAGRAPHS

The following is a marked-up version of the Specification's replacement paragraphs pursuant to 37 C.F.R. §1.121(b) with instructions and markings showing changes made herein to the previous version of record of the Specification. Underlining denotes added text while bracketing denotes deleted text.

IN THE SPECIFICATION

On page 1, amend the paragraph beginning on line 2 as follows:

This application claims the benefit of priority of United States Provisional Application Serial No. 60/084,850 to Judith A. Varner, filed May 8, 1998, now abandoned, and entitled A NOVEL METHOD FOR THE DETECTION AND INHIBITION OF ANGIOGENESIS, the entire contents of which [is] are incorporated herein by reference.